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REVIEW Open Access

Eliminating dog-mediated rabies: challenges and strategies

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Abstract

Rabies is an acute encephalitis caused by a *lyssavirus*. It is primarily transmitted through bites of infected dogs which results in the worldwide death of an estimated 59000 humans every year. The disease is preventable through the application of post-exposure prophylaxis (PEP) and its elimination has been demonstrated in many countries by applying multiple interventions simultaneously. Nonetheless, rabies is still widespread in many developing countries, primarily due to the poor implementation of intervention strategies that include inadequate dog-bite wound management practices, unavailability/unaffordability of PEP by the communities, failure to control the disease in free-roaming dogs and wildlife, improper dog population management, weak surveillance and diagnostic facilities and a lack of a One Health approach to the disease. In this review, strategies to control dog-mediated rabies through a One Health approach were discussed. We recommend applying multiple interventions against the disease by involving all the concerned stakeholders in selected urban and rural areas of the countries where rabies is endemic. An empirical demonstration of disease freedom in the selected areas through a One Health approach is needed to convince policymakers to invest in rabies prevention and control on the national level. This multifaceted One Health control model will enhance the likelihood of achieving the goal of global rabies eradication by 2030.

Keywords: Rabies, Dog-mediated rabies, Dog-bites, Strategies, Challenges

Background

Rabies and its relationship with dog-bites have been known to humans since prehistoric times (Baer 1991). The disease is known for emerging in geographical areas where it was never present, and remerging in places where it was previously controlled or eradicated (Rupprecht et al. 2002).

The annual mortality of the disease in humans has been estimated at 59000 with the socially and economically disadvantaged sectors of society being the most vulnerable (Barbosa Costa et al. 2018; Regea 2017; Tiwari et al. 2019a). It is primarily maintained and transmitted through the bites of Free-Roaming Dogs (FRD) (Isloor et al. 2020) and is widespread in countries that either do not have legislation regulating movement and ownership of dogs or do not implement them strictly (Özen et al. 2016; Taylor et al. 2017). Although wild carnivores and bats are the natural reservoirs of rabies virus, it is the domestic dog, *Canis lupus familiaris*, that usually acts as the most common host and chief source of infection for humans (World Health Organization 2018).

Rabies occurs worldwide except for several isolated islands and countries where it has never been reported or in several countries that have been successful in eradicating the virus (WHO 2018b). However, in these countries there is a constant threat of introduction/re-introduction through infected animals or a spill over event from infected wildlife (Castrodale et al. 2008). The death of individuals in rabies-free countries has been

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reported due to recent exposure of the victims when visiting endemic countries (Meslin 2005).

The countries most affected with rabies are the developing nations in Asia and Africa, while it is also endemic in some South American nations (Ortiz-Prado et al. 2016). Poor availability of post-exposure prophylaxis, lack of awareness about the disease, frequent misdiagnosis with similar encephalitic diseases, inefficient FRD management, along with the lack of adequate infrastructure and surveillance capacity are the salient reasons for such high endemicity in these countries (Wallace et al. 2017a, 2017b).

The global strategy to fight dog-mediated rabies has been characterised by different approaches by countries depending upon the availability of resources, the priority given to the disease by the government and the level of awareness of it by the public. A combined effort to provide direction and impetus to the actions of countries towards the elimination of dog-mediated rabies was launched in 2018 (World Health Organization 2018). The Global Action Plan (GAP) constitutes a rabies elimination centred platform supported by the World Health Organisation (WHO), the Food and Agriculture Organization (FAO) and the World Organisation of Animal Health (OIE). Aptly called 'United Against Rabies' (UAR), these three organisations are collaborating towards the fruition of common objectives to eliminate the disease from the world by 2030 (Rupprecht et al. 2020).

In this review, we take account of the challenges of eradicating dog-mediated rabies in countries where it is endemic. After elaborating on the human-canine relationship, rabies epidemiology, and the need for sustained surveillance, we briefly describe the challenges faced by these countries towards the implementation of effective interventions. The possible strategies and One Health approach towards elimination of dog-mediated rabies were also discussed (Fig. 1).

Humans and the domestic dogs

Humans domesticated dogs (*Canis lupus familiaris*) more than 10000 years ago (Clutton-Brock 1999). Dogs play significant roles in human lives (Clutton-Brock 1995; Hiby 2013) owing to their behavioural traits, physical attributes and most importantly due to their proclivity for human proximity (Hiby 2013; Bräuer et al. 2013; Udell and Wynne 2008). Nonetheless, the attitudes of people towards dogs varies (Hiby 2013) and the literacy level, socio-economic status, and religious-cultural practices collectively influence a societies' and individual's association with dogs (Otolorin et al. 2014). For rabies to establish and flourish, there needs to be ample interaction between canine populations (Amaral et al. 2014). To assume that no interaction takes place between a pet dog that is owned and FRD would be incorrect as pet dogs may be under various levels of movement restriction (Slater 2001). Practically, the term pet dog could mean anything from a dog fully dependent on humans to various degrees of dependence for food and shelter based on the level of restriction placed on its movement (Cliquet and Barrat 2012). Rapid urbanisation has led to restricted living spaces and forced abandonment of litters of pet dogs by urban dog owners (Castillo-Neyra et al. 2017; Butcher 1999; Krishna 2009). In addition, uncontrolled breeding has also increased numbers of FRD leading to the emergence of several public health concerns (Krishna 2009; Otranto et al. 2009). FRDs have been widely reported to have multiple adverse effects on society, such as spreading litter due to their scavenging habits, agonistic behaviour towards humans, and wildlife deaths in fringe areas by transmitting pathogens and predation (Beck 1975; Belsare and Gompper 2013; Pal et al. 1998). As a competent reservoir host of many

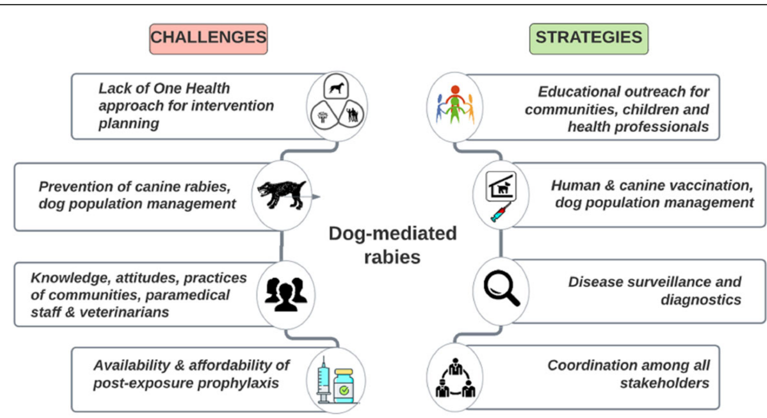

Fig. 1 Diagrammatic representation of challenges and strategies for elimination of dog-mediated rabies in countries where the disease is endemic

zoonotic agents, dogs pose a potential threat to animal welfare (Otranto et al. 2009), but their role in transmitting rabies has had the greatest impact in developing countries in terms of human death and economic burden (Traub et al. 2005; Ratsitorahina et al. 2009).

Rabies

Rabies is an acute encephalitis or meningoencephalitis caused by an infection with a *lyssavirus* (WHO 2013). The virus is one of more than 20 identified variants, all of which affect mammalian hosts and are zoonotic (Crowcroft and Thampi 2015). Belonging to the family *Rhabdoviridae* of order Mononegavirales, it can infect a wide range of hosts that include bats, foxes, raccoons and canids, but dogs are the greatest source of rabies infection for humans (Rupprecht et al. 2002).

(a) *Transmission*

The usual natural route of transmission occurs through a bite from a reservoir animal (Dietzschold et al. 2008). Although the virus cannot penetrate intact skin, it can gain ingress through scratches, open wounds, or direct exposure across mucous membranes (Crowcroft and Thampi 2015). Other reported routes of infection include consumption of affected carcasses by arctic foxes (*Vulpes lagopus*) or through inhalation of aerosols, either in a laboratory setting (Winkler et al. 1973) or from caving in areas with a large population of bats (Dietzschold et al. 2008). Although the virus may be present in body fluids, such as lacrimal gland and tracheal secretions, and tissues such as pharynx, skeletal muscles, liver, kidney and skin during the first 5 weeks of illness, infected humans are generally dead-end hosts (Helmick et al. 1987). However, human-to-human transmission has been reported in corneal transplant recipients (Crowcroft and Thampi 2015; Helmick et al. 1987), and in the case of four recipients of organs from a common donor who died of rabies (Srinivasan et al. 2005).

(b) *Incubation*

Rabies virus (RABV) has a variable incubation period in humans that ranges from of 5 days to several years (Rupprecht 1996). The incubation period is influenced by three factors: the amount of virus in the inoculum; the nerve motor endplate density at the wound site; and the proximity of the virus entry to the central nervous system (Ugolini 2007; Hemachudha et al. 2013). After introduction, before it enters the peripheral nervous system, the virus evades peripheral immune system recognition (Rupprecht 1996). On entering the unmyelinated axon terminals, it is transported into nerve cell centripetally in a retrograde manner. The virus replicates in nerve cell and reaches brain after spreading through the chain of neurons connected by synaptic junctions. After infecting the central nervous system, it moves centrifugally to the peripheral and autonomic nervous systems and finally reaches salivary glands where it can be shed (Dietzschold et al. 2008). Speed of the migration depends on the mode of propagation as centripetal retrograde movement is faster than the centrifugal mode (Hemachudha et al. 2013). Rabies in humans involves either the urban cycle with dog populations maintaining the infection or the sylvatic form which involves wildlife. There is documented evidence of it moving from domesticated dogs to wildlife and vice-versa (Gongal and Wright 2011).

(c) *Epidemiology*

Although RABV are among the most feared *lyssaviruses* associated with bats, interestingly, except for the Americas, it has not been detected in both bats and terrestrial carnivore species in other regions of the world (Banyard et al. 2014). In most endemic countries, RABV is maintained by circulation in wild carnivores, but the domestic dog is the principal host responsible for transmitting the disease to humans (Bengis et al. 2004). The disease has largely been eliminated from western Europe, North America, Japan and some Latin American countries through mass immunisation of the principal hosts, such as dogs and foxes, along with population control of wildlife reservoirs such as raccoon dogs, wolves and skunks (Finnegan et al. 2002; WHO 2018a); however, it still has a dominating presence in many developing countries of the Caribbean, Asia and Africa (WHO 2017; Hampson et al. 2015; Wandeler 2011). Most human deaths due to rabies are reported from Asia and Africa, and the majority of these are due to the transmission of variants of canine RABV (Nagarajan et al. 2006). Many Pacific Island nations and Australia have never reported the presence of canine rabies (Carrara et al. 2013).

(d) *Prevention and Control*

Human mortality arising from dog-associated rabies can be minimised through the following strategies: by administering post-exposure prophylaxis to exposed individuals; by vaccinating a sufficient number of dogs to interrupt the transmission cycle; or by a combination of both strategies (Taylor and Nel 2015). Vaccination of people against rabies involves pre-exposure and post-exposure schedules. Pre-exposure vaccinations are recommended for individuals who are at a higher risk of infection, such as wildlife professionals, veterinarians and dog catchers, although post-exposure vaccination is still required after potential exposure to the virus. Post-exposure vaccination is administered to individuals after they have had potential exposure to a rabid animal (Briggs 2012). The post-exposure management of the bite wound comprises washing and adequate flushing of the bite wound, followed by administration of a series of post-bite vaccines and infiltration of Rabies Immunoglobulins (RIG) into/around the site of the bite, as soon as possible after the exposure (WHO 2018a). There have been significant advances in the development of rabies vaccine from 'Pasteur-treatment' to Cell Culture Vaccines (CCV)/Purified Chicken Embryo Cell Vaccines (PCECV) and Purified Duck Embryo Vaccines (PDEV) (Briggs 2012).

Rabies is one of the earliest diseases for which canine vaccination was introduced with the first mass vaccination campaign of dogs reportedly undertaken in Japan in 1920 (Briggs 2012). Dogs are the largest reservoir host for RABV and many researchers recommend that at least 70% dog population needs to be immunised to eliminate canine rabies (Franka et al. 2013; Coleman and Dye 1996). In contrast, it has been suggested that owing to the lower basic reproduction number (R_0) for rabies, vaccination coverage of even 35% dog population may be sufficient to eliminate it from this population (Fitzpatrick et al. 2016).

Parenteral vaccination of FRD, when undertaken effectively (ruling out vaccine failures due to faulty inoculation or a break in the cold chain process), induces a robust immune response and is the first choice for vaccination (WHO 2018b). However, accessibility of FRD for vaccination is difficult due to the challenges of finding them and then catching and restraining them, which can result in the handlers being bitten or injured, or the dogs themselves suffering an injury (Cliquet et al. 2007). Thus, the target of achieving 70% "herd-immunity" remains elusive in many areas that have a large FRD population. The latest report of the WHO consultations on rabies advocates the use of Oral Rabies Vaccination (ORV) to complement parenteral coverage (WHO 2018b). Oral rabies vaccination has contributed to the successful elimination of fox-rabies from Europe (Freuling et al. 2013) although its efficacy to evoke an adequate immune response in FRD is not assured owing to immunological and delivery concerns.

The story of effective ORV in wildlife in Europe spans four decades of progressive development of various vaccine types and intervention strategies since its first use in Switzerland in 1978. Although the attenuated rabies virus (SAD Bern, RV-97) vaccines are the most widely used, others types, such as selected monoclonal antibody escape mutants vaccines (SAD VA1, SAG1 and SAD2), were developed through reverse genetics (ERA 333); and the recombinant vaccinia virus expressing glycoprotein from ERA strain (V-RG), are also available (Müller et al. 2015). Nonetheless, success of ORV is influenced by the timings and frequency of interventions and the kind of baits used. Besides the selection of appropriate baiting requirements, such as embedding the vaccines in meat or egg-based decoys, dogs are required to chew the sachet/blister containing vaccine for the latter to be correctly deposited into the oral mucosa. Furthermore, replication of the modified live or recombinant construct vaccine is essential to evoke an immune response in the host. Despite these challenges to the use of ORV, the benefits of using ORV to immunise FRD that are not accessible for parenteral vaccination is recommended (Cleaveland et al. 2006; WHO 2018b)

Challenges of rabies control

Years of research resulted in the development of tools required for the eradication of rabies; however, freedom from rabies has not been achieved in countries of Africa, Asia and South America where known tools were rarely applied simultaneously (Franka et al. 2013). People in these regions generally lack awareness about rabies, which is exacerbated by the expense of rabies vaccine, particularly for low-income groups with an inadequate health care system.

The reasons for such sporadic application of the interventions could be due to lack of awareness about the disease; misplaced or other priorities; perceived scanty incentive for undertaking rabies eradication as the true burden of disease remains elusive (Maroof 2013); a lack of studies on the population dynamics and behaviour of FRD; and weak or non-existent coordination between different players concerned with the rabies control programmes, such as the government, medical/veterinary agencies and non-governmental organisations (Scott et al. 2017; Garcia et al. 2018; Rock et al. 2017). While the basic strategy for rabies control to eliminate human mortality is based on two interventions, namely, (a) to provide access to the post-exposure anti-rabies vaccination to the dog-bite victims and (b) to mass-vaccinate at least 70% dog population against rabies; there is a multitude of societal, economic, or cultural factors and impediments to implementing these.

(a) *Knowledge, attitudes and practices*

Several studies assessing the community's awareness of canine mediated rabies in endemic countries through knowledge, attitudes and practices (KAP) studies have resulted in an overall improvement in the community's knowledge of the disease; however, gaps in the knowledge and misinformation regarding the disease remain, especially in the rural and socio-economically poor sectors of the community (Tiwari et al. 2019b). Not surprisingly, crucial information about the disease eludes the most vulnerable populations, such as school-age children, families with children less than 14 years of age and religious groups that support FRD in the human settlements (Madjadinan et al. 2020; Tiwari et al. 2019a). Besides the lack of knowledge about the disease, misplaced attitudes of the communities in endemic countries persist regarding post-bite management of wounds, such as applying traditional therapies and belief in local priests to provide relief through religious rituals (Singh et al. 2020; Jemberu et al. 2013). Another cause of concern is a lack of knowledge about rabies and post-bite management of wounds by the frontline medical staff. In a recent study in the north-central African country of Chad, significant knowledge gaps were reported in the medical as well as veterinary health professionals regarding almost all aspects of the disease, including its prevention, transmission and treatment (Mbaipago et al. 2020).

In addition to the gaps in the knowledge of rabies, misplaced attitudes, and perception of the community towards dogs, especially the FRD, also contribute to the rabies prevalence but is, unfortunately, a less explored aspect. For example, a study on rural communities in western India indicated that feeding the FRD was rather due to the strong religious beliefs of the residents than any genuine concern for the latter's welfare and that although livestock owners were likely to have positive attitudes towards FRD welfare they were less likely to feed them than other community groups (Tiwari et al. 2019c). The attitudes of the communities also affect the welfare of FRD, including their health and longevity (Totton et al. 2010; Paul et al. 2016). Rabies is the most important zoonotic disease to be transmitted by FRD, but research has also highlighted their roles in the spread of other zoonoses including leptospirosis, echinococcosis, toxocariasis, cutaneous and visceral larval migrans (Traub et al. 2005).

In rural India, dogs mostly "belong" to the partially owned category, where, although a household may have a claim to their ownership, these people do not consider themselves responsible for the animal's vaccination and veterinary care (Tiwari 2019). In contrast, in African countries, it has been easier to achieve a higher mass vaccination level of FRD, with owners willing to vaccinate their dogs, although they were not amenable to keeping them restrained/restricted (Dürr et al. 2008). With the second highest human mortalities due to rabies, control strategies of canine rabies in China is weakened due to reported disparity in the vaccination coverage between the registered dogs and unowned FRD (Miao et al. 2021). In rural China, family guard dogs, along with unowned dogs, remain unregistered, and hence are rarely, if ever, vaccinated against rabies (Tian et al. 2018).

The practices of the communities regarding the management of dog bite wounds, including their reliance on traditional healing leads to higher incidence of the disease in rural and remote localities. There is evidence to suggest that a majority of dog bite victims in developing countries apply turmeric, chilli powder or lime before they seek formal medical treatment, which in many instances causes a crucial delay for the administration of PEP (Ghosh et al. 2016; Ghosh et al. 2020; Tiwari et al. 2019d). A lack of optimal bite-wound washing has also been reported among the frontline medical staff (Tiwari et al. 2018b). While adequate wound washing with soap and water for a minimum of 20 min can reduce the incidence of rabies by 65%, most medical staff in developing countries are not trained in this aspect of dog-bite wound management (Burki 2008). Further, the lack of proper dissemination of knowledge by the paramedical staff about the importance of completing the full regimen of anti-rabies PEP also leads to poor compliance by dog-bite victims (Changalucha et al. 2019). These practices all contribute to the higher incidence of human disease in rural and disadvantaged communities.

(b) *Availability and affordability of post-exposure prophylaxis (PEP)*

Variability in the availability of PEP outside urban centres is a significant barrier against rabies in low- and middle-income countries (Sreenivasan et al. 2019). Even as the problem of remoteness is being addressed by many countries ensuring the availability of PEP at local levels (Tiwari et al. 2018b), the challenges of lack of storage facilities, maintenance of cold chain and inaccurate forecasting of the amount required in rural areas remained (Abela-Ridder et al. 2016). Few studies have explored alternatives to the absence of a cold chain as a barrier to transporting and stocking PEP in remote health facilities (Madjadinan et al. 2020).

Some countries where rabies is endemic, however, have reported the inability to provide free PEP due to limited financial capacity. The lack of financial support for rabies prevention and control by governments is a crucial shortcoming contributing to the non-availability of PEP at rural health centres and hence the effective control of rabies in humans (Wentworth et al. 2019). In other instances, lack of cold chain facilities for long-distance supply has been cited as the reason for the unavailability of anti-rabies vaccines in remote rural areas (Joseph et al. 2013). In addition to these shortcomings, non-compliance to the vaccination and PEP schedule by persons who have been bitten also contributes to mortality due to rabies, despite the presence of available preventive measures (Changalucha et al. 2019).

(c) *Prevention of canine rabies*

It is imperative to control rabies in dogs to prevent human deaths from this disease. The number of human deaths is high in countries with an unregulated dog population and where the disease is widespread. In contrast, it has been successfully controlled in most developed countries through mass vaccination of canines along with concerted public awareness efforts (Kallo et al. 2020). However, emulation of such efforts in the developing nations of Asia and Africa is countered with several obstacles including, not only the lack of awareness about the disease on the part of pet owners, and the large FRD populations, but also due to a lack of sufficient studies on dog population dynamics, movement and behaviour that govern the ecology of the disease transmission in FRD (Lembo et al. 2010). Unfortunately, a substantial part of efforts to control rabies in dogs is devoted to controlling dog population through expensive animal birth control measures rather than vaccinating dogs (Knobel et al. 2013). Nonetheless, the success of a mass-vaccination drive depends on an accurate estimation of the population size of FRD (Tiwari et al. 2018a, 2018b). The pack behaviour and movement of dogs are also important to effectively determine the combination of oral and parenteral vaccination required to achieve 70% inoculation, as inaccessibility of FRD for vaccination is a serious impediment that hinders reaching the adequate level of immunisation (Tiwari 2019).

(d) *Lack of a One Health approach*

Rabies control calls for a truly One Health approach, where elimination of it in dogs can prevent human mortality. While on one hand, implementation of mass vaccination of dogs and population management of FRD can break the transmission cycle of RABV. There are other factors, such as sustained educational outreach, the economics of vaccine procurement, and concerted efforts by the medical and veterinary authorities, that require supporting by the administrative authorities and policymakers (Fitzpatrick et al. 2016). The paucity of funds and a lack of relevant data on the burden of rabies lowers the priority compared with other diseases for a nation's/region's policymakers (Kakkar et al. 2012). For example, only registered dogs are required to be vaccinated in China, as per the nation's policy on control of rabies. Consequently, despite the second highest number of human deaths due to dog-mediated rabies in the world, it is difficult to convince veterinarians to vaccinate unregistered dogs, especially in rural areas (Tu et al. 2018). Nevertheless, the onus to generate empirical evidence regarding the plausibility of elimination of dog-mediated rabies through the One Health approach lies with the ecologists, veterinarians and public health scholars. Few studies have obtained empirical data on such a comprehensive One Health approach that can assess the success or highlight its shortcomings.

Strategies for control of dog-mediated rabies

(a) *Educational outreach*

The promotion of awareness about rabies is one of the foundational pillars of any strategy to eliminate rabies. The importance of enhancing the understanding of it has been emphasised over the past few decades in communities of countries where the disease is endemic. Although the general awareness of the disease has increased, there remain gaps in the way the dog-bite wounds are managed, and early provision of PEP is sought. The negative attitudes of communities towards FRD in these countries also needs to be altered. Educating communities about the need for better welfare for FRD and promotion of responsible ownership of dogs should form part of rabies awareness drives. There are vulnerable groups, such as children, who remain bereft of essential information about the disease. The educational outreach drives should include such vulnerable groups in their ambit. Further, the lack of application of preventive practices for bite wound management or PEP compliance could be attributable to little refresher training of paramedical staff (Penjor et al. 2020). Hence, educational outreach programs must be sustained and not one off-exercises.

Awareness programmes can achieve full potential if they are organised in tandem with canine mass vaccination drives, as this would involve larger participation by the community whereby people who regularly feed these dogs would be able to get them vaccinated, in addition to understanding the importance of canine immunisation for rabies elimination. Another recommendation is to introduce rabies and dog welfare into the curriculum of school children. Being the most vulnerable group, they could be primed early, not only about the dangers of dog-bites, but also about the welfare of FRD. The creation of e-learning modules for the stakeholders including children, para-medical staff and veterinarians could be a better way than undertaking face-to-face activities, as they can reach a wider population and can be repeated without any major logistical requirements. Information can be circulated through social media for wider and faster distribution and potential impact.

(b) *Human, canine anti-rabies vaccination and dog population management*

Rabies is preventable if a dog-bite victim is provided PEP within 48 h of the bite. The poor affordability of the anti-rabies vaccines has been addressed in China and

Kenya by including the cost of PEP in the insurance scheme for medical claim settlement or by their free provision (Liu et al. 2017; Wambura et al. 2019). While there could be an improvement in the delivery of anti-rabies vaccines in remote areas through efficient forecasting, the challenge of cold chain maintenance at the stockists and local vaccines centres could be mitigated by incentivising the local pharmacists with refrigeration facilities. Solar energy powered refrigeration units could be adopted to maintain the cold chain in remote areas where other sources of energy are unavailable.

The costs and the number of visits to the clinic for PEP can be reduced by following the newer, short intradermal vaccination regimen which now is recommended by WHO (Rupprecht et al. 2020). However, the recommended change in the route (from intramuscular to intradermal) and regimen (only three injections to complete the full schedule) requires large-scale advocacy by the user countries. A strategy that supports expedited adoption of the updated schedule will help reduce the total vaccine costs and ease the non-availability of PEP. The application-based (APP) approach through mobile phone technology has been suggested to monitor PEP compliance by dog-bite victims (Mtema et al. 2016). We recommend studies are undertaken that can model the likely PEP requirement in an area based on variables such as: size of FRD population; group forming behaviour; and retrospective data on the frequency of dog bites.

It was admitted during a recent meeting to discuss the strategies for rabies elimination in Asia-Pacific that reduction in the expenditure on human PEP cannot be achieved until there is confirmation that local FRD are free of RABV (Rupprecht et al. 2020), which is possible through mass-vaccination of this population. However, mass vaccination of the recommended 70% FRD is not achievable without prior estimation of their population size and thereafter assessing the logistics of vaccinating all dogs. Based on the production levels in 2015, Wallace et al. (2017a, 2017b) calculated that US $3.9 billion was required to vaccinate 70% dogs in all countries where the disease is endemic. It is unrealistic to expect a commitment of such funds for canine mass-vaccination when in countries, such as India, the disease is not notifiable and is certainly not priority for control (Radhakrishnan et al. 2020). Further, there are barriers to the success of such immunisation campaigns, especially in countries where most of FRD are inaccessible for parenteral vaccination (Gibson et al. 2020). WHO advocates ORV under supervision to supplement the injectable vaccination effort (WHO 2018b). However few studies have evaluated the economic cost of ORV for rabies control.

Despite WHO recommendations regarding the use of ORV to immunise FRD, albeit under supervision, lessons can be drawn from the successes of ORV in Europe to eliminate wildlife rabies. It could not be solely attributed to the widely used first generation ORV (SAD rabies isolates). While there was no significant difference in the efficacy between the vaccine types (SAD B-19, SAG2 and V-RG), Müller et al. (2015) highlighted the importance of vaccination strategy for effective vaccination coverage. The use of ORV for FRD in low-income countries should take into consideration the spatio-temporal overlaps of FRD home ranges, kind of baits used, and efficient distribution of ORV in the target areas. As there are few examples of the application of ORV in countries where rabies is endemic, we recommend studies be undertaken to evaluate the suitability of different types of ORV and associated strategies for ensuring adequate uptake of the vaccine by FRD. Such studies may also emphasise development of region-specific immunogenic vaccines.

In a previous publication, we advocated investment in studies on FRD behaviour and demography to forecast the required combination of oral and parenteral vaccines in canines for rural and urban localities (Tiwari 2019; Tiwari et al. 2019b). In a country, such as India, where the average longevity of an individual FRD is estimated to be only 2.8 years (Totton et al. 2010), maintaining immunity level against rabies in dog population to break virus transmission will require several canine mass-vaccination campaigns over multiple years.

It is recommended that vaccination of FRD against rabies is preceded by a dog enumeration survey to ensure that adequate vaccination doses are sourced to vaccinate at least 70% population. In the absence of a gold standard population estimation technique for FRD, the accurate assessment of their population size for 70% vaccination coverage is difficult and could lead to failure of the immunisation programmes (Wallace et al. 2017a, 2017b). A novel approach called Application Super Duplicates (AS), which estimates at least up to 70% of the true FRD population, was recommended in a previous study conducted in India (Tiwari et al. 2018a). Adopting the AS technique, which requires only two sight-resight surveys, is a reliable way to obtain a population estimate that can guide, not only the logistics before vaccination campaigns, but also help achieve herd immunity in FRD against rabies (Tiwari et al. 2019e).

In addition to increasing the awareness level of the community on the dangers of having FRD which can act as transmitters of rabies and other zoonotic diseases; dog population management in countries with a large uncontrollable population of FRD, such as India, need a different dimension. Three cardinal aspects of this new strategy would be (a) unique identification of individual dogs, (b) establishment of dog shelter homes and (c) attaching a “value” to the FRD by making them useful to society. It is now possible to have an identity database of all dogs in an area, along with their vaccination history, through machine learning applications (McGreevy et al. 2019). The need for individual human PEP following a dog bite could be assessed as FRD involved in the incident could be identified and its vaccination history confirmed from the database. The judicious use of PEP by administering only those victims where the identity of the biting dog is unavailable will augment the availability of PEP.

Secondly, in addition to being a constant threat of transmitting RABV, FRD are also a social nuisance being a cause of littering, other zoonotic infections, and road accidents (Rinzin et al. 2017). Such untoward incidents are also detrimental to FRD welfare but can be controlled by establishing dog pounds or shelters where such dogs could be housed. While an assessment of FRD prior to housing would be required to minimise the disadvantages of such compulsory kennelling, adoption or rescue from established dog pounds will be beneficial towards the financial efforts of erecting and managing such dog-pounds (Miller and Zawistowski 2015). Community opposition for such establishments is likely but increasing general community awareness of canine transmitted zoonoses and improved welfare of FRD could be used to change the community's perceptions about restricting FRD to shelters.

Finally, it is important to explore the trainability of FRD. The lack of concern for such dogs is possibly due to no value being attached to them compared to pedigree dogs. It was established in a KAP assessment study by Tiwari et al. (2019a) in the urban location of Panchkula in north India that communities assume responsibility for vaccination of owned pedigree dogs but not for FRD adopted off the streets. This may arise because pedigree dogs are purchased/gifted and are thought to be more intelligent and useful than FRD (Tiwari et al. 2019a). In contrast, the perception about FRD is that they are not useful and hence even if when adopted/owned, the owners are unwilling to invest in their health. Such community behaviour could potentially be changed if the usefulness of FRD is demonstrated. This could be achieved by conducting studies to explore the positive behavioural traits of FRD and establishing their societal utility. Possibly, a comparative study of the performance of FRD vis-à-vis pedigree dogs could dispel the myths of poor intelligence about the former. The tools used to assess the socially accepted behaviour (SAB) of owned dogs could equally be applied to the FRD to assess their suitability for training (Villa et al. 2017). Unfortunately, few studies have been conducted to date addressing these issues, although we feel that assessing the usefulness of FRD will increase their social acceptability and enhance their adoption rate.

(c) *Surveillance and diagnostics*

Inconsistent reporting, poor infrastructure, lack of trained personnel and weak disease communication to vulnerable communities characterise the absence or minimal existence of standardised and systematic surveillance of animal diseases and zoonosis in the countries that report the highest incidence of rabies (Mbilo et al. 2020). A One Health based surveillance approach that has a clear disease and case definition for rabies and is ably supported by a network of laboratories catering to vulnerable areas, including rural and remote localities, has been suggested as a mandatory requirement for the elimination of rabies (Franka and Wallace 2018). A sound surveillance system is considered integral to estimating the true disease burden and initiating change in the health policy for the control of rabies (Mollentze et al. 2013). A crucial aspect of rabies surveillance in many countries is the under-reporting of the disease in livestock (Thiptara et al. 2011; Hampson et al. 2015). This could be due to livestock owners not reporting the disease, coupled with the absence of laboratories capable of diagnosing it (Wallace et al. 2015). Furthermore, sample transportation for diagnosis from remote rural areas is also a challenge. Diagnosis of the circulating RABV in livestock could potentially be an early sign of an impending outbreak, especially in fringe areas of national parks/forested areas where a spill-over from the sylvatic cycle is a possibility.

The development of diagnostic infrastructure in countries where the virus is endemic is an economic challenge, however, there are rapid, simple to perform tests that can be undertaken in the field. The Lateral Flow Assay (LFA), which is an indirect ELISA, is a useful diagnostic tool for detection (Kimitsuki et al. 2020; Yale et al. 2019), with a 94.6% sensitivity compared with the gold standard direct fluorescent antibody test (dFA). Conducting this indirect ELISA test requires minimal training, although the process of sample extraction requires skill; however, field veterinarians could easily be trained in this procedure. Provision of LFA kits to remote localities could assist in obtaining robust data for assessing disease burden, as well as providing valuable evidence of the proximity of a rabid dog.

While the need for accuracy of diagnosis is mandatory, another aspect that can enhance rabies surveillance is strengthening disease communication using an e-connectivity platform for all stakeholders. The central database could be maintained by the health/veterinary officials and all stakeholders, including community members, could be encouraged to be a part of this system and to report any FRD displaying suspicious clinical signs. The information could then be passed to dog rescue teams or municipal authorities in real-time who would arrange to remove the dog from community potentially before anyone is bitten. The system could also incorporate a dog identification component to monitor FRD movement. Online platform could also serve as the repository for related information on rabies, PEP and responsible dog-ownership, along with the 'dos and don'ts' for dog owners as well as general public. It could also contain the list of dog pounds in the area and their contact details for general public to approach them whenever a FRD is sighted or to inform the pound of a dog bite on a human. This information could then be used by the respective dog pound to facilitate the catching, testing and restriction/sheltering of the relevant FRD.

(d) *Coordination*

There has been a huge emphasis on international cooperation between countries to eliminate dog-mediated rabies, as it is well established thatit is not confined by national boundaries (Feng et al. 2015; Trewby et al. 2017). Although the efforts at the international level, including formation of UAR is commendable, rabies intervention at the local level is often deficient. Rabies control programmes in endemic countries often face poor coordination on the part of the stakeholders and a difference of opinion on whether the responsibility for rabies control should lie with the health authorities or with the agriculture departments (Wallace et al. 2017a, 2017b). A cross-disciplinary network that integrates the efforts of physicians, veterinarians, ecologists, public health workers, animal welfare workers, educational institutes, social scientists, and administrative authorities is essential to effectively combat dog-mediated rabies (Anderson and Shwiff 2015; Buchy et al. 2017; Lavan et al. 2017). Furthermore, it has been reported that communities have an inherent belief that the responsibility of mass vaccinations of FRD lies with the governments and not with the residents who occasionally provide the dogs with food and shelter (Tiwari et al. 2018b; Tiwari et al. 2019a). Such expectations could be addressed through undertaking canine mass vaccination programs, while also using the occasion to promote sheltering of FRD in dog pounds by educating the residents regarding public health hazards of having unrestricted dogs in their neighbourhood.

Surprisingly, a contrary school of thought exists where authors advocate 'peaceful coexistence' of FRD with humans and describe the latter as scavengers of human refuse and thus important for human settlements (Majumder et al. 2014). In India, where Animal Birth Control (ABC) has been a government-approved policy for dog population management and rabies control, the de-sexed dogs are released back into the localities from where they were originally caught instead of relocating them to dog shelters (Gupta and Gupta 2019). However, the volume of edible waste produced in urban centres has increased and has led to a complex human-animal interface that includes FRD and other scavenging species such as pigs, kites and stray cattle, which facilitates a perfect milieu for potential emergence and spread of rabies and other zoonotic diseases (Kumar et al. 2019). We recommend stronger advocacy towards policies that can efficiently address the issue of edible waste disposal and the possibility of emerging zoonotic diseases by avoiding human-animal and inter-species conflict in urban areas.

Conclusions

In addition to the central role of medical and veterinary stakeholders, we believe that a tangible rabies elimination plan warrants participation by ecologists, social scientists, animal welfare enthusiasts, schoolteachers and most importantly the administrative authorities. A concerted effort by all concerned is required to devise and implement a comprehensive intervention strategy that includes mass vaccination of FRD; management FRD population; garbage management; sustained educational outreach to children; increased scope and frequency of awareness campaigns; incentives to encourage people to adopt FRD and develop responsible ownership behaviours; and increasing the availability of PEP to all community members. Furthermore, a robust surveillance system that would enable reporting and testing of deceased FRD through use of low-cost diagnostic kits is integral to an intervention programme. Public-private partnerships must be encouraged to explore and exploit the usefulness of FRD, incentivise their adoption and promote responsible ownership of dogs. It is only when an all-round effort is made by applying multiple interventions over time in targeted areas that this ancient fatal disease, which despite being preventable results in the deaths of more than 59000 humans each year, can be eradicated. Conducting a pilot project to adopt a One Health approach in selected urban and rural areas of countries where rabies is endemic would provide the necessary data and empirical evidence to convince decision-makers on the benefits of initiating large scale nationwide rabies eradication programmes.

Abbreviations

PEP: Post-exposure Prophylaxis; FRD: Free Roaming Dogs; WHO: World Health Organisation; GAP: Global Action Plan; FAO: Food and Agriculture Organisation; OIE: World Organisation of Animal Health; UAR: United Against Rabies; RABV: Rabies Virus; RIG: Rabies Immunoglobulins; CCV: Cell Culture Vaccines; PCECV: Purified Chicken Embryo Cell Vaccines; PDEV: Purified Duck Embryo Vaccines; R_0: Reproduction Number; ORV: Oral Rabies Vaccine; KAP: Knowledge, Attitudes and Practices; AS: Application SuperDuplicates; LFA: Lateral Flow Assay; dFA: Direct Fluorescent Antibody Test; ABC: Animal Birth Control

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